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THE EFFECT OF GB ON THE RAT'S BLOOD PRESSURE

By

P. DIRNHUBER AND H. CULLUMBINE

PORTON TECHNICAL PAPER No. 365

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The Effect of GB on the rat's blood pressure

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P. Dirnhuber and H. Cullumbine

SUMMARY

GB, DFP, eserine, TEPP and E.600 all produce hypertension when administered to rats in near-lethal doses. The mechanism of production of this hypertension has been studied. It is, apparently, due to a central mechanism acting via the sympathetic nervous system on the blood vessels of the skin.

(Sgd.) H. Cullumbine,
Head, Physiology Section.

(Sgd.) E. A. Perren,
Superintendent, Research Division.

PD/HC/SP

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Introduction

In recent species studied (e.g. rabbit, cat, monkey, dog) the effect of a systemic intoxication with GB is the production of a profound fall in blood pressure. Wilson has analysed the mechanisms responsible for this hypotensive action.

We have recently noticed that GB, when given intravenously in near lethal doses (40 - 60 ug/kg.) to intact rats, produces a sharp rise in blood pressure, then one or two oscillations about the point of increased pressure, followed by a very gradual fall in pressure over the next several minutes (10 - 180 minutes in different animals) back to the pre-injection level (Figure 1). The course of this sustained rise in blood pressure produced by GB has been investigated.

Methods

White rats of homogenous strain and weighing 350 - 500 g. were used. They were anaesthetised with urethane (1.25g./kg. subcutaneously) and polythene canulae inserted into the carotid artery, to record blood pressure, and into the femoral vein.

With the doses of GB used respiratory embarassment or failure may occur and may interfere with the blood pressure recording or response. Therefore, in many cases, even respiratory exchange was maintained throughout by means of a miniature starting "Ideal" pump. The same pattern of cardiovascular response has, however, been seen in rats which were not sustained by artificial ventilation.

Spinal preparations were made by transecting the spinal cord between C1 and C2 and pithing the brain.

Results:- The hypertensive effect of GB is best seen following a fairly large dose (40 - 60 µg/kg.) but is still evident with smaller doses. The effects of rapidly repeated small doses can be summated up to a certain point and then the general blood pressure level falls although each

successive GB dose produces a transient, small rise (Figure 2). With higher doses of GB (e.g. 90 µg/kg) the animal dies before the sustained rise in blood pressure has become established (Figure 3).

Bilateral vagotomy does not affect the picture (Figure 4), but if GB is given to a spinal rat only a relatively slow, small and short lasting increase in blood pressure is caused (Figure 5).

The failure of GB to produce a sustained elevation of blood pressure in this case is not due to the low blood pressure presented by a spinal rat. Thus, if the blood pressure is lowered by bleeding (Figure 6) or by C6 (Figure 10). GB still produces a typical hypertensive blood pressure response.

This suggests that GB is stimulating a central mechanism and this stimulation is probably a cholinergic phenomenon since in the previously atropinized cat (intact or spinal) GB produces again only a slow and minor rise in blood pressure (Figure 7). Similarly, if successive doses of atropine are administered after the GB, a step-like depression of the elevated blood pressure is produced (Figure 8).

If hexamethonium bromide (C6) is given to a rat during the phase of sustained blood pressure rise following GB, the blood pressure is immediately and temporarily reduced (Figure 9). Pre-treatment with C6 before administering the GB does not prevent the usual blood pressure response to the latter (Figure 10).

The central stimulant action of GB is effected, therefore, via the sympathetic nervous system. The liberation of adrenaline from the adrenal glands would not seem to be important since GB still causes an increased blood pressure in adrenalectomized rats (Figure 11) and this can be inhibited by C6.

A sympathetic peripheral vascular mechanism is probably involved since peripheral blockade of sympathetic impulses with ergotamine or Priscol does alter the response to GB. If either of these substances is administered before GB, the latter produces only a preliminary sharp rise, but no sustained elevation of blood pressure (Figure 12). If GB is given first and then Priscol during the period of raised blood pressure, the latter is at once temporarily reduced (Figure 13).

The sustained rise in blood pressure induced by GB is probably due mainly to constriction of the skin arterioles; in the skinned rat, GB causes only an immediate and temporary rise in pressure, but no continued elevation is seen (Figure 14). In conformity with this is the observation that GB produces a maintained pressure rise when administered to an eviscerated rat (Figure 15). This rise is not as long lasting as that occurring in the intact rat, so that some involvement of the arterioles of the splanchnic area may be present.

That a direct action on a central mechanism is involved is also suggested by the observation that a small dose (5 ug) of GB, injected into the fourth ventricle, causes a similar sustained rise in blood pressure (Figure 16). An injection of acetyl choline into the same site

produces a fall in blood pressure (Figure 17). The dissimilarity in the actions of acetyl choline and GB may be due to a failure of the former to penetrate into the brain substance, although some leakage into the systemic circulation occurs. The direct central action of the GB can still be prevented by systemic atropinization (Figure 18).

The hypertensive action of GB in the rat is not peculiar to that compound, but is shared by other anti-cholinesterases, e.g. DFP (Figure 19), eserine, TEPP, E.600, and probably many others. Atropine and C6 will affect the response to these agents in the manner described for GB.

Another indication of the enhanced sympathetic tone in these rats is that the heart rate (measured via the E.C.G.) is increased during the period of hypertension e.g. in a typical instance:

Heart rate before GB (40 µg/kg.) - 270/minute

Heart rate during phase of rising blood pressure - 390/minute

Heart rate at peak of blood pressure rise - 450/minute

In other species where a fall of blood pressure is produced by GB, this is accompanied by a slowing of the heart rate (Wilson (1)).

Discussion:- From the above results we can conclude that GB, when given intravenously to the rat, produces a rise in blood pressure which is due to a central action, possibly via the vasomator centre. The effect is not seen in the spinal rat, nor following atropine. The latter observation suggests that the action is probably a cholinergic phenomenon involving the centre.

The central stimulation presumably acts via the sympathetic nervous system and this sympathetic "drive" can be blocked at the ganglia by hexamethonium bromide and also more peripherally by ergotamine or Priscol. It would appear that the vessels of the rat's skin are those chiefly concerned in this sympathetic action.

Other anticholinesterases can produce a similar hypertension in the rat, so that the phenomenon presumably has the inhibition of cholinesterase as its basis. The rise in blood pressure is, further, not peculiar to the intravenous route of administration since it has also been seen after the intraventricular or the intracarotid injection of GB.

In other species GB, when administered intravenously in near-lethal doses, causes a profound lowering of the blood pressure. The latter is accompanied by a marked slowing of the heart and vasodilatation of the small vessels in the limb muscles (Wilson, (1); Holmes (2)). If, however, GB in small doses is injected into the vertebral artery or the cisterna magna of a dog, a rise in blood pressure is the invariable response (Wilson, (3)). Therefore a hypertensive response via a central mechanism can be seen in another species than the rat. In the dog, following intravenous administration, it must be presumed that the peripheral effects of GB on the cardiovascular system predominate over the central stimulating action, although a transient rise of B.P. is often observed before the profound fall takes place. This applies equally to the sheep (Wilson (4)).

These varying responses in the different species suggest that there may be corresponding differences in the nature and the sensitivity of the receptor substances and the cholinesterases of the tissues of these species. This is being further investigated.

Summary

GB, DFP, eserine, TEPP and E.600 all produce hypertension when administered to rats in near-lethal doses. The mechanism of production of this hypertension has been studied. It is, apparently, due to a central mechanism acting via the sympathetic nervous system on the blood vessels of the skin.

(Sgd.) H. Cullumbine,
Head, Physiology Section.

(Sgd.) E.A. Perren,
Superintendent, Research Division.

References

(1) Wilson, K.M. P.T.P. 152.

(2) Holmes, R. P.T.P. 356.

(3) Wilson, K.M. Personal communication.

(4) Wilson, K.M. and Birnhuber, P. P.T.P. 346.

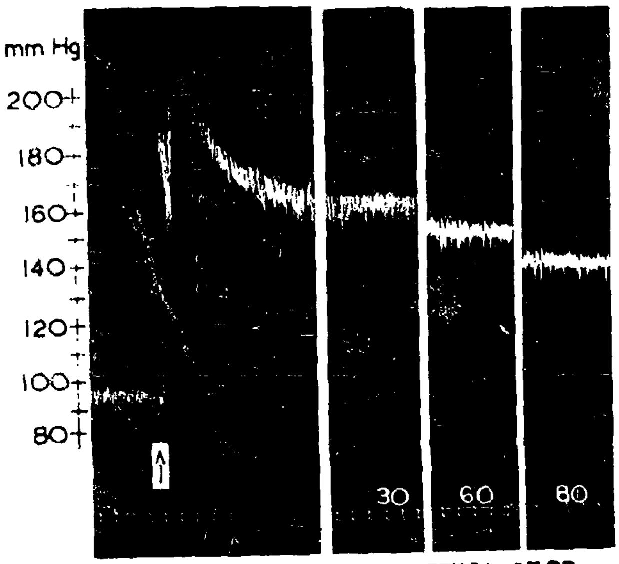

FIG 1. HYPERTENSIVE EFFECT OF GB.
Rat 370g. Urethane.
Spontaneous respiration
at arrow 40μ GB/kg intravenously.

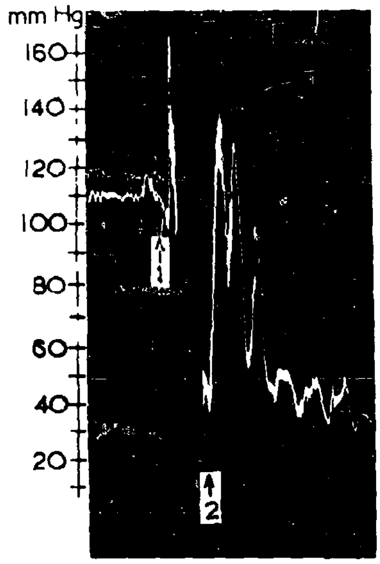

FIG.3. HIGHER DOSE OF GB.
Rat 420g. Urethane.
90 μg GB/kg intravenously at arrow 1. Interrupted artificial ventilation after arrow 2.

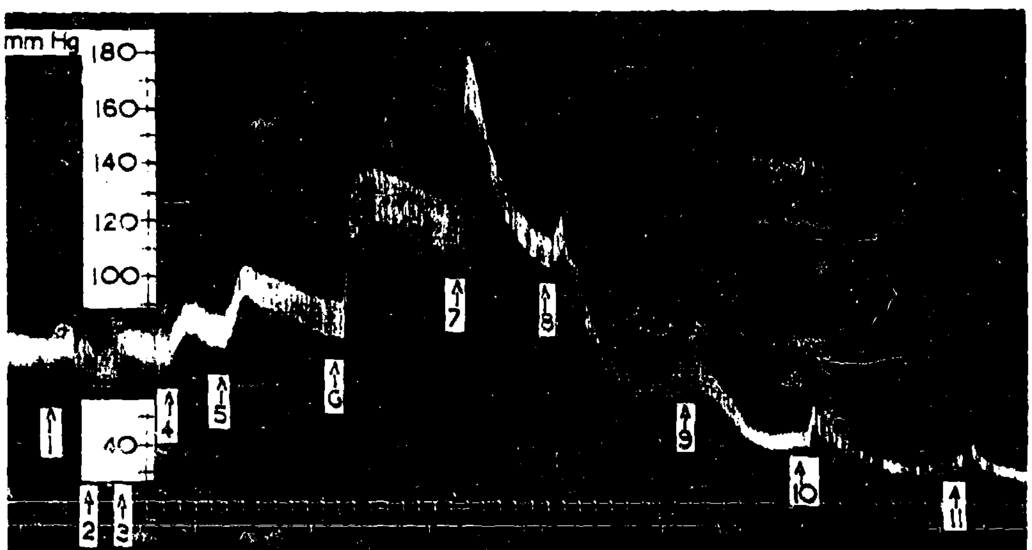

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FIG. 2. REPEATED SMALL DOSES OF GB
Rat 400g. Urethane. Artificial ventilation.
At each arrow 5μ GB/kg intravenously.
(Total of II doses)

Time signal 1 minute intervals

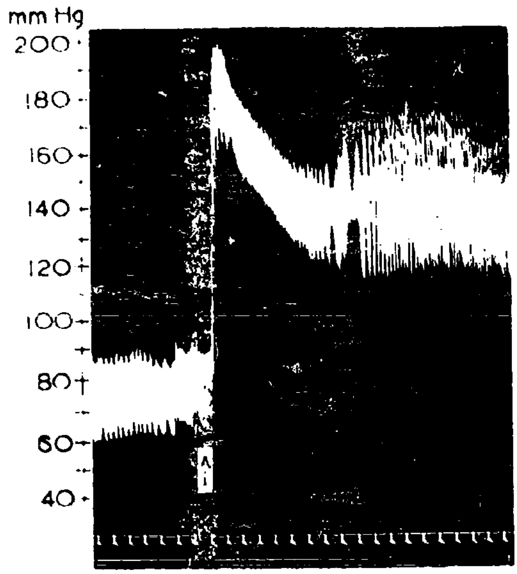

FIG.4. RESPONSE NOT AFFECTED BY VAGOTOMY.

Rat 400g. Urethane. Both vagi cut, carotid artery tied. Artificial ventilation. At arrow 40μg GB/kg intravenously.

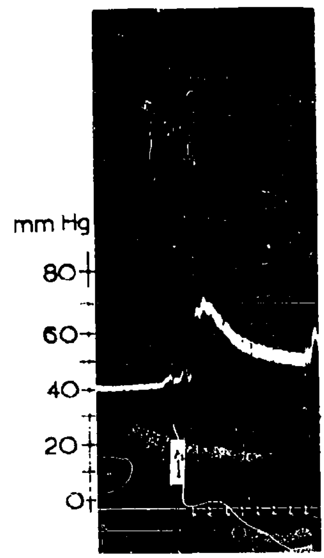

FIG.5 SMALL RISE IN SPINAL RAT.

Rat 470g Urethane. Spine transsected, brain pithed. At arrow 40μg GB/kg intravenously.

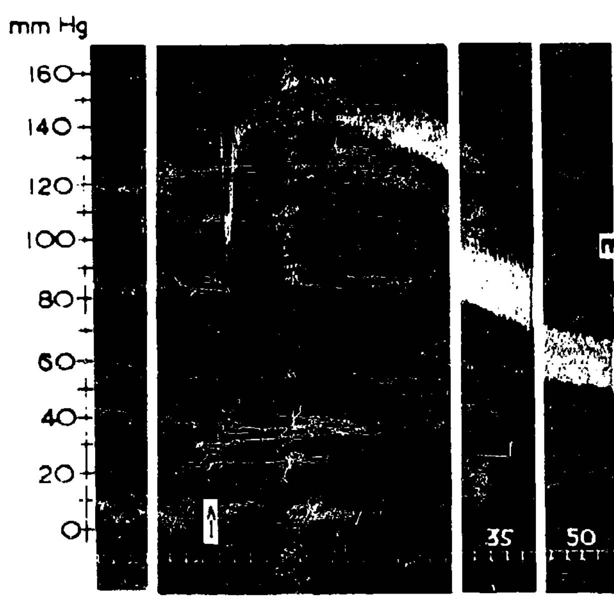

FIG.6. TYPICAL PRESSOR RESPONSE AFTER EXSANGUINATION.

Rat 470g Urethane. Artificial ventilation 6ml. blood withdrawn between strip 1 & 2. At arrow 40μg GB/kg intravenously.

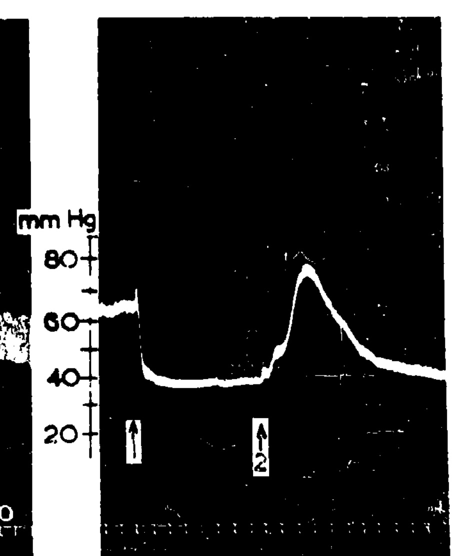

FIG.7 SMALL RISE IN ATROPINISED ANIMAL

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Rat 310g Urethane
Artificial ventilation
At arrow 1 10 mg ATR/kg
At arrow 2 40μg GB/kg intravenously.

Time signal 1 minute intervals

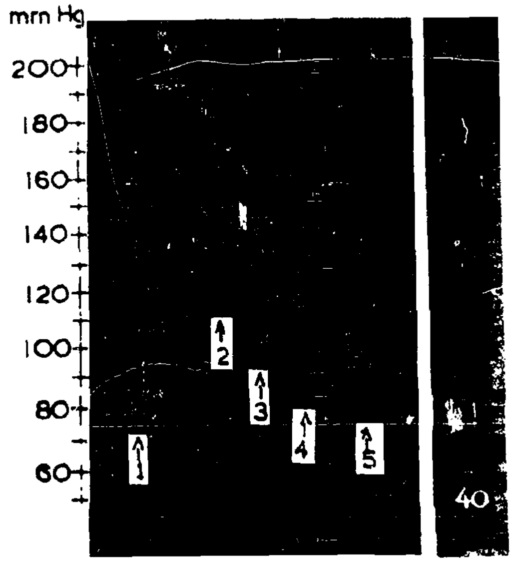

FIG. 8. ATROPINE LOWERS ELEVATED B.P.
Rat 420g. Urethane. Artificial ventilation.
At arrow 1 40µg CB/kg i.v.
At arrows 2 to 5 each 0·5mg ATR/kg i.v.

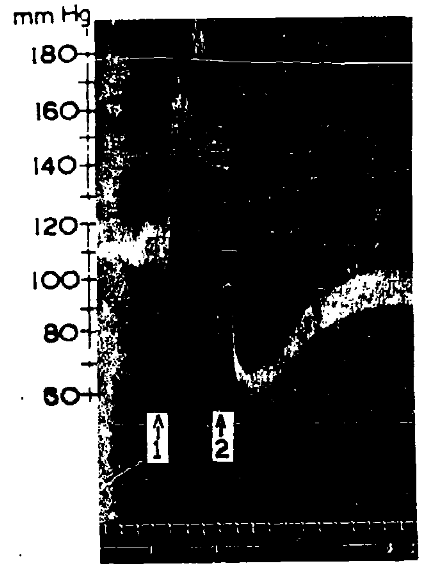

FIG. 9. C6 AFTER CB REDUCES B.P.
Rat 390g. Urethane.
Artificial ventilation.
At arrow 1 40µg CB/kg.
At arrow 2 10mg C6/kg.
intravenously.

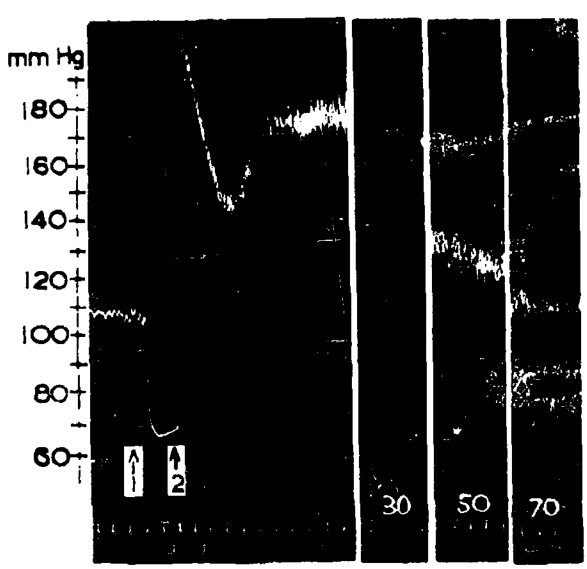

FIG. 10. PRE-TREATMENT WITH C6.
TYPICAL PRESSOR RESPONSE BY CB
Rat 390g. Urethane. Spontaneous respiration
At arrow 1 20mg C6/kg } intravenously.
2 60µg CB/kg

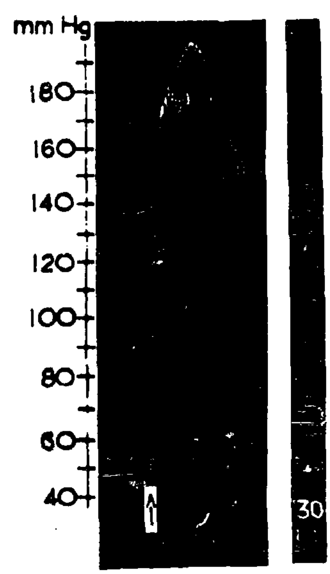

FIG. 11.
PRESSOR RESPONSE UNAFFECTED BY ADRENALECTOMY.
Rat 480 g. Urethane.
Artificial ventilation.
Both adrenals removed.
At arrow 40µg CB/kg
intravenously. T.936/3.

Time signal 1minute intervals

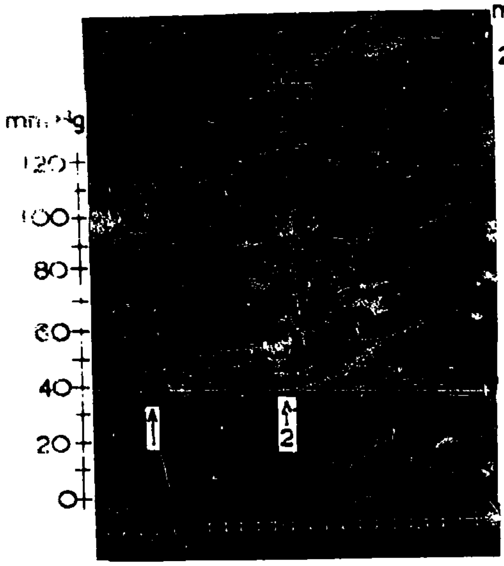

FIG.12. PRE-TREATMENT WITH PRISCOL
SMALL PRESSOR EFFECT

Rat 390g Urethane
Artificial ventilation
At arrow 1 10mgPRI/kg
At arrow 2 40µgGB/kg

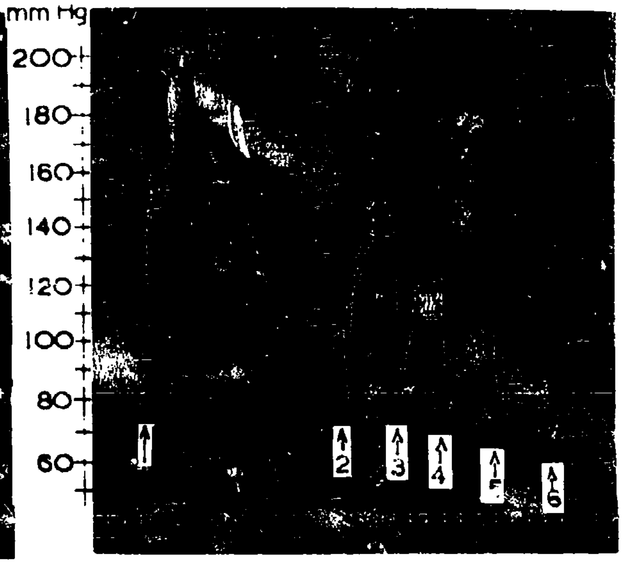

FIG 13. PRISCOL LOWERS ELEVATED BP
Rat 470g Urethane Artificial ventilation
At arrow 1 40µgGB/kg
At arrows 2 to 5 each 1 mg PRI/kg
all intravenously

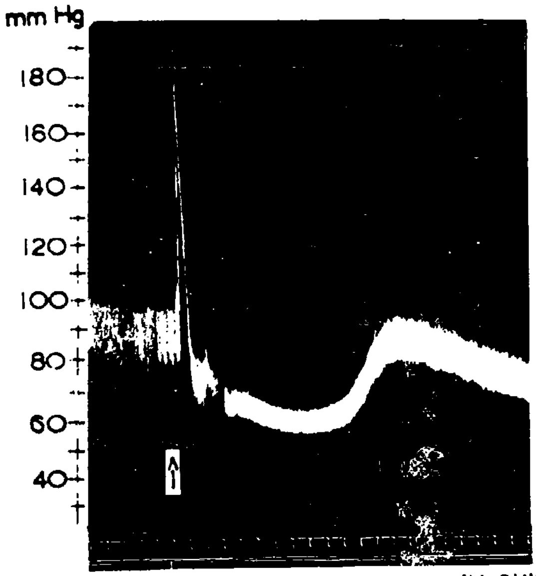

FIG 14 NO CONTINUED ELEVATION IN SKINNED ANIMAL
Rat 480g Urethane Artificial ventilation
All skin removed (head, feet & scrotum not skinned)
Body placed in saline bath of 37°
At arrow 40µgGB/kg intravenously.

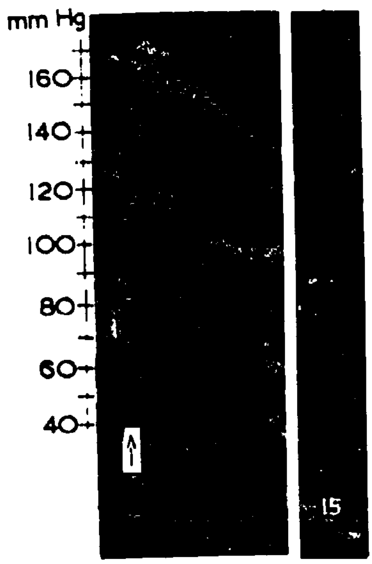

FIG.15. MAINTAINED ELEVATION IN EVISCERATED ANIMAL.
Rat 390g. Urethane.
Artificial ventilation
Small and large intestines removed.
At arrow 40µg GB/kg i.v.

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Time signal 1minute intervals

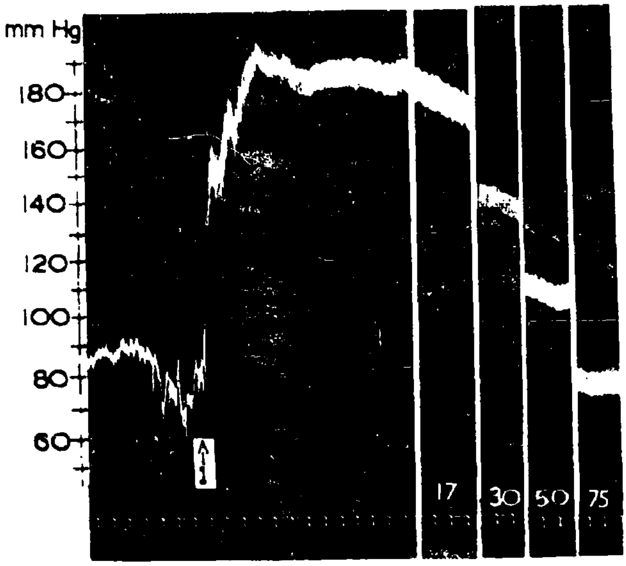

FIG. 16. SMALL DOSE OF GB INTO 4th VENTRICLE
Rat 420g. Urethane. Artificial ventilation.
At arrow 5 μg GB/rat through atlanto-occipital membrane

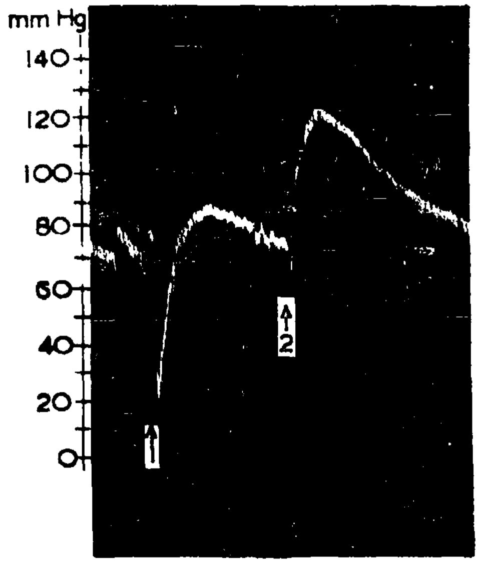

FIG. 17. OPPOSITE EFFECT OF ACh AND GB ON INJECTION INTO 4th VENTRICLE
Rat 370g. Urethane.
Artificial ventilation.
At arrow 1 2 μg ACh/rat
At arrow 2 5 μg GB/rat
both through atlanto-occipital membrane.

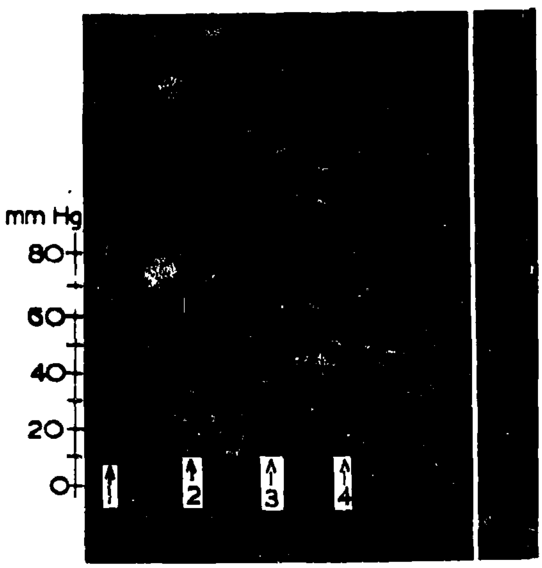

FIG. 18. PRE TREATMENT WITH ATROPINE INHIBITS PRESSOR RESPONSE TO INTRAVENTRICULAR GB
Rat 350g. Urethane. Artificial ventilation.
At arrow 1 2 μg ACh/kg }
2 2mg ATR/kg } intravenously.
3 2mg ACh/kg }
4 5 μg GB/rat into ventricle.

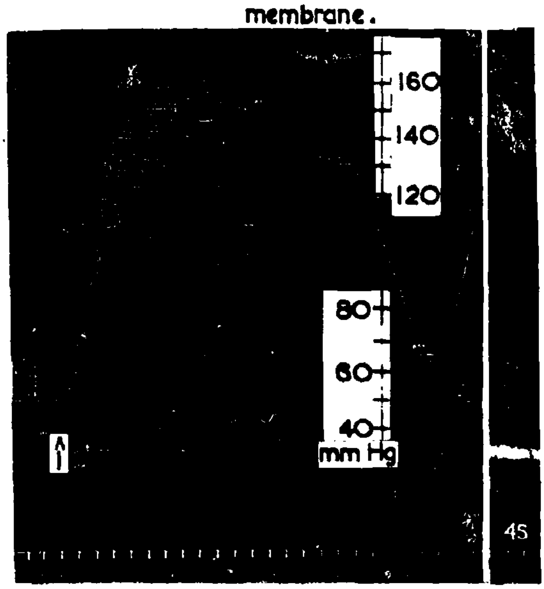

FIG. 19. HYPERTENSIVE EFFECT OF DFP.
Rat 470g. Urethane. Artificial ventilation.
At arrow 1mg DFP/kg intravenously.

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Time signal 1minute intervals

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